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(54) THERAPEUTIC COMBINATIONS OF FATTY ACIDS

THERAPEUTISCHE KOMBINATIONEN VON FETTSÄUREN

COMBINAISONS THERAPEUTIQUES D'ACIDES GRAS

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Description

[0001] There are two series of essential fatty acids (EFAs) in humans. They are termed "essential" because they cannot be synthesised de novo in mammals. Their metabolic pathways are shown in figure 1. These fatty acids can be interconverted within a series, but the omega-6 (n-6) series cannot be converted to the omega-3 series nor can the omega-3 (n-3) series be converted to the omega-6 series in humans. The main EFAs in the diet are linoleic acid of the omega-6 series and alpha-linolenic acid of the omega-3 series. However, to fulfil most of their biological effects these "parent" EFAs must be metabolised to the other fatty acids shown in figure 1. Each fatty acid probably has a specific role in the body. Particularly important in the n-6 series are dihomo-gammalinolenic acid (DGLA, 20:3n-6) and arachidonic acid (AA, 20:4n-6), while particularly important in the n-3 series are eicosapentaenoic acid (EPA, 20:5n-3) and docosahexaenoic acid (22:6n-3). This patent specification particularly concerns combinations of AA and EPA.

[0002] AA is found as an important constituent of all cell membranes and particularly of cell membranes of nerve cells. It is an important component of many signal transduction systems which are activated by many different forms of cell stimulation. AA is usually found in cells in the form of phospholipids. Cell activation generates a range of active phospholipases which can release AA as the free acid. The free acid has many direct actions of its own in regulating protein kinases and other enzymes, in modulating movements of calcium and other ions, in activating receptors such as peroxisome proliferator activated receptors (PPARs), and in modulating gene function. Furthermore AA can be converted to an enormous range of even more active derivatives known by the general name of eicosanoids. These include prostaglandins, leukotrienes, thromboxanes, various types of hydroxy acids, lipoxins, hepxilins and many other compounds. These substances are often involved in inflammatory and thrombotic reactions and are frequently regarded as harmful in their overall effects. This harmful image is illustrated by the fact that intravenous AA is frequently lethal because of its thrombotic effects, and by the fact that the steroids which are widely used, in particular for their anti-inflammatory effects, block the release of AA by phospholipases. Moreover, the class of drugs known as cyclo-oxygenase inhibitors, which include aspirin and many other well known compounds, known for their antithrombotic and anti-inflammatory effects, inhibit the conversion of AA to prostaglandins and thromboxanes.

[0003] This concept of the potential toxicity of AA has become well established. The expert organisation in the field, the International Society for the Study of Fatty Acids and Lipids (ISSFAL) in 1999 organised a workshop in association with the US National Institutes of Health. The remit of the workshop was to make recommendations concerning the human uses of EFAs. The participants, all leading experts in the field, had no doubts about the harmful effects of AA, and emphasised this in their final statement (AP Simopoulos et al, Essentiality of and recommended dietary intakes for omega-6 and omega-3 fatty acids, Nutrition and Metabolism 1999; 43:127-130). The ISSFAL newsletter reporting on this workshop stated that "after much discussion, consensus was reached on the importance of reducing the omega-6 polyunsaturated fatty acids (PUFAs) even as the omega-3 PUFAs are increased in the diet of adults and newborns for optimal brain and cardiovascular function. This is necessary to reduce adverse effects of arachidonic acid and its eicosanoid products".

[0004] In contrast to this general view of AA toxicity, the experts of ISSFAL and NIH were keen to promote the value of the n-3 EFAs, particularly EPA and DHA for human health. The view was taken that EPA and DHA would replace AA in cell membrane phospholipids and also reduce AA synthesis from linoleic acid. The lowering of AA levels by EPA and/or DHA was expected to have widespread beneficial effects on human health.

[0005] The present invention results from recent surprising observations of the inventor which suggest that this view may be wrong. Contrary to the general expert opinion, it has now been found that AA is highly desirable rather than undesirable and it may be helpful to administer AA in association with EPA. The present invention provides this combination treatment.

[0006] The present invention provides use in the manufacture of a medicament for the treatment of a neurological degenerative disorder of a composition consisting essentially wholly of eicosapentaenoic acid or any appropriate derivative (hereinafter collectively referred to as EPA) and arachidonic acid (AA) or any appropriate derivative, as set out in the claims attached hereto. AA may be replaced by one or more of its precursors, DGLA or GLA. The EPA and AA (or precursor) has a purity of at least 90%. The ratio of EPA to AA is between 1:1 and 20:1.

[0007] The EPA is preferably provided in a dose of between 100 mg and 10,000mg/day. The formulation may be a single preparation comprising 100-10,000 mg EPA. An alternative upper limit is 5,000 mg EPA. Preferably, the formulations of the invention comprise 1 - 4 g EPA and 0.1 - 2.0 g arachidonic acid (AA). Still preferred amounts are 1.5 - 3g EPA and 0.2 - 1g AA.

[0008] The formulation may be a single daily dose preparation to give in one dose the above intakes, or may be in convenient divided doses, for example, a daily dose formed of four soft gelatin or other capsules, each containing 500 mg of EPA in an appropriate form and 150mg of AA in an appropriate form.

[0009] The compositions used in the present invention are prepared by combining EPA in biologically assimilable form in which the EPA is at least 90% pure, and arachidonic acid (AA) in any biologically assimilable form in which the AA is at least 90% pure.

[0010] Flavourants or emulsifiers may be included to make the preparation palatable. Other conventional additives, diluents and excipients may be present. The preparation for ingestion may be in the form of a capsule, a dry powder, a tablet, an oil, an emulsion or any other appropriate form. The capsules may be hard or soft gelatin capsules, agar capsules, or any other appropriate capsule.

[0011] The EPA is preferably composed of a triglyceride or ethyl ester which is more than 90% pure. Other forms of the fatty acids which may be useful include the free acids, salts, esters of any type, amides, mono-, di- or triglycerides, phospholipids or any other form which can lead to the incorporation of EPA into body tissues. If phospholipids are considered, it is specifically excluded from the present invention that a phospholipid containing two different fatty acids, that is containing both EPA and AA (or AA precursor) is used. Phospholipids containing EPA may however be used in the present formulations when combined with phospholipids containing AA or AA precursor.

[0012] The medicaments made by the present invention may be used for the treatment of any neurological degenerative disorders, including a degenerative disorder of the brain, Alzheimer's disease and other dementias and Parkinson's disease.

[0013] The treatment or preventative method using the medicaments is, for example, by the combined application of EPA and AA at the dosage regime of between 100mg and 10,000mg/day EPA and a ratio of EPA to AA of between 1:1 and 20:1. A precursor to AA, selected from DGLA and GLA, may be used instead of AA. The preferred range of EPA to AA (or its precursor) is between 1:1 and 5:1.

[0014] The specific therapeutic compositions proposed are ones which provide not less than 100mg and not more than 10,000mg of EPA/day combined with AA, DGLA or GLA, in doses of between 100mg and 10,000mg/day. An alternative upper limit is 5,000 mg/day of the fatty acids. Particularly preferred amounts are 1-4g per day EPA combined with 0.1 - 2.0 g per day arachidonic acid, or one of its precursors, GLA or DGLA. A still preferred composition comprises 1.5 - 3g EPA and 0.2 - 1g AA. Use of the present invention further provides a medicament, for example, in a one-a-day dose comprising 1.5 - 3 g EPA and 0.1 - 2.0 g arachidonic acid or one of its precursors.

[0015] The ratio of EPA to the omega-6 fatty acid is important because too much EPA is likely to lead to the loss of AA from membranes, while too much AA may lead to adverse effects because of excessive conversion of AA to eicosanoid. The ratio of EPA to AA or DGLA or GLA should therefore never be less than 1:1, should be in the range between 20:1 and 1:1, and should still preferably be in the range of between 5:1 and 1:1. These combinations will ensure that the beneficial effects of EPA are enhanced and maintained even at relatively high EPA doses, because the provision of AA and its precursors will prevent AA depletion which may occur when too much EPA is given alone.

[0016] During absorption from the gut and within the body, EPA moieties are readily transformed intact from one chemical form to another. Simple esters such as ethyl or methyl esters are readily split by esterases and the freed fatty acids can then be bound by albumin or other binding or transport proteins or incorporated into complex lipids such as phospholipids, cholesterol ester or glycerides. The fatty acids in the present formulations can therefore be administered in any form such as glycerides, esters, free acids, salts, phospholipids, amides or any other form which leads to their incorporation into the blood and cell membranes.

[0017] The EPA, AA, DGLA or GLA may be derived from any appropriate source including plant seed oils, microbial oils from algae or fungal or marine oils from fish or other marine animals. They may be purified to give products containing 90% or more of the fatty acid. A particularly useful form of EPA is the highly purified ethyl ester described in patent filings based on the preliminary UK filing 9901809.5. Synthetic routes to the fatty acids are also possible although at present are not economically feasible.

[0018] Once the oils containing the individual fatty acids have been obtained and purified, the starting materials may be blended to give the desirable ratios of EPA to AA, DGLA or GLA described above.

[0019] The blended fatty acid compositions may then be incorporated into any appropriate dosage form for oral, enteral, parenteral, rectal, vaginal, dermal or other route of administration. Soft or hard gelatin capsules, flavoured oil blends, emulsifiers or other liquid forms, and microencapsulate powders or other dry form vehicles are all appropriate ways of administering the products.

Example Formulations

[0020]

(a) Soft or hard gelatin capsules each containing 500mg or 1000mg of a mix of 10 parts 95% pure ethyl-EPA to 2 parts of 95% pure AA;

(b) As in (a) but where the AA and EPA ethyl esters are replaced with the fatty acids in any other appropriate bioassimilable form such as the free acid, tri-, di- or monoglyceride, other esters, salts such as the sodium, potassium or lithium salts, amides, phospholipids or any other appropriate derivatives;

(c) As in (a) or (b) but where the EPA or EPA derivative is 90% pure and where the AA or AA derivative is 90% pure;

(d) As in (a)-(c) but where the ratio of EPA to AA is anywhere in the range from 1:1 to 20:1;

(e) As in (a)-(d) but where the material is in the form of a microencapsulated powder which can be used as a powder or compressed into tablets. Such powders may be prepared by a variety of technologies known to those skilled in the art;

(f) As in (a)-(d) but where the formulation is a liquid or emulsion, appropriately flavoured for palatable oral administration;

(g) As in (a)-(d) but where the material is formulated in to material appropriate for topical application such as a cream or ointment;

(h) As in (a)-(g) but where the AA is replaced by one of its precursors, GLA or DGLA.

Brief description of the figures

[0021]

Fig 1. the metabolic pathways of the two series of essential fatty acids.

Experimental Data

[0022] A trial was conducted of the administration of a placebo and three different doses of EPA, 1g, 2g and 4g/day in the treatment of schizophrenia in patients who were also taking the antischizophrenic drug clozapine. Previous pilot studies had suggested that EPA would have desirable effects and the expectation was that the higher the dose of EPA, the better would be the effect. 31 patients were entered into the study and followed for 12 weeks. They were assessed at baseline and 12 weeks using the Positive and Negative Symptom Scale for Schizophrenia (PANSS). The percentage improvements from baseline are shown in table 1. Placebo produced a small effect, 1g/day produced a larger effect, 2g/day produced a large effect of 26.0% compared to the usual 15-20% improvements on this scale generated by existing drugs for schizophrenia. It was expected that 4g/day would produce the best effect but this did not happen. The effect of 4g/day while there, was substantially less than the effect of 2g/day, and comparable to that of 1g/day.

Table 1. Percentage improvements from baseline to 12 weeks on the Positive and Negative Symptom Scale for Schizophrenia (PANSS) in patients given placebo, 1g/day, 2g/day or 4g/day ethyl eicosapentaenoate

	Placebo	1g	2g	4g
n	7	9	9	6
Improvement	6.0%	18.3%	26.0%	16.3%

[0023] In these patients, and also in a further series of patients, the levels of DGLA, AA, EPA and DHA were measured in human red cells before starting treatment and after 12 weeks. The results were partly expected and partly surprising and are shown in table 2. As expected there was a dose-related rise in EPA which was greater the greater the dose. It was also expected that there would be a progressive decline in AA, the larger the EPA dose, the greater the fall in AA. However, this did not happen. 1g/day of EPA produced a small rise in AA while 2g/day produced a large rise. 4g/day EPA produced the expected fall in AA.

Table 2. Changes from baseline to 12 weeks in red cell concentrations (in $\mu\text{g/g}$) of eicosapentaenoic acid (EPA) and arachidonic acid (AA) in red blood cells in four groups of schizophrenic patients given placebo or 1g/d, 2g/d or 4g/d ethyl-EPA. + means a rise and - means a fall

	Placebo	1g	2g	4g
EPA	-0.6	+2.4	+33.7	+49.0
AA	-12.6	+2.7	+29.4	-26.5

[0024] It appeared that the improvement in schizophrenic symptoms was more related to the changes in AA than to

the changes in EPA. This was tested in a larger series of patients where the improvement in PANSS was correlated with the changes in all the major EFAs. The values for r , the correlation coefficient, are shown in table 3 as is the statistical significance of the relationship. An r value of 1.0 means that the two parameters are perfectly related while one of 0.0 means that there is no relationship whatsoever.

Table 3. Correlations between the change from baseline to 12 weeks on the total PANSS score and the change from baseline to 12 weeks in the red cell concentration of various essential fatty acids. r , the correlation coefficient from a linear regression analysis, is shown. p is the statistical significance of the relationship.

Fatty acid	Correlation coefficient r	Significance p =
Dihomogammalinolenic (DGLA)	-0.51	0.09
Arachidonic (AA)	-0.81	0.001
Eicosapentaenoic (EPA)	-0.07	0.84
Docosapentaenoic (DPA)	-0.12	0.76
Docosahexaenoic (DHA)	-0.35	0.13

[0025] From the table it is clear that by far the strongest relationship is with AA, and the second strongest relationship is with DGLA. Rises in these two fatty acids are strongly associated with improvement in schizophrenic symptoms, as indicated by a fall in the PANSS score, hence the negative correlations. In contrast there is almost no relationship with EPA because high doses of EPA are associated with falls in red cell AA levels and the loss of clinical effect.

[0026] These results were completely unexpected. Far from EPA itself being the most desirable fatty acid in cell membranes it seems that AA and DGLA are more helpful. The likeliest interpretation of this is that AA is desirable when it is retained in membrane phospholipids and not converted to potentially dangerous eicosanoids. The effect of EPA may be to inhibit phospholipases and so keep AA in the phospholipid form. Very high doses of EPA, however, displace AA and the therapeutic effect is lost.

[0027] This interpretation was supported by a pilot study in which AA itself was given to five patients with schizophrenia. The expectation was that they would improve, but in fact their condition deteriorated. The administration of AA, without EPA to inhibit phospholipases, may lead to increased formation of eicosanoids rather than to incorporation of AA into phospholipids.

[0028] The conclusion to be drawn from these studies is that EPA is desirable, not in itself but because it raises the AA level in membrane phospholipids. High doses of EPA, far from being valuable in themselves, may be undesirable because they lead to excessive loss of AA from membranes. The way to get around this issue, and to boost the clearly desirable effects of EPA, is to keep to relatively low doses of EPA, but also to boost the level of AA by administering the EPA with either AA or one of its precursors, DGLA or gamma-linolenic acid GLA. When AA in a dose of 1g/day was given to two patients who had already been taking 2g/day EPA for 3 months, they experienced a substantial further improvement without any of the worsening seen when AA was given alone.

[0029] US Patent 4,977,187 provided for combinations of n-3 fatty acids and n-6 fatty acids and vitamin E in the treatment of schizophrenia. However, that patent did not direct attention to AA specifically or to EPA specifically, or to the specific combination of EPA with AA or its immediate precursors or to the specific doses and ratios of EPA and AA described in this specification. Any n-6 fatty acid could be combined with any n-3 fatty acid in any ratio in US 4,977,198 and corresponding patents.

[0030] A review of the literature suggests that the phenomenon described here is not only true of schizophrenia but of several disorders where EPA is therapeutically useful. There are many studies describing the value of low doses of EPA containing products in cardiovascular diseases, in inflammatory disease and in other disorders. However, when investigators have gone to higher doses, these desirable therapeutic effects have been lost. To take two examples, high doses of EPA completely failed to exert beneficial effects in patients undergoing angioplasty for coronary vascular disease, or in patients with inflammatory bowel disease, even though earlier studies with smaller EPA doses had given strong evidence of benefit. The authors had no real explanation for the trial failure and did not consider the possibility that excess depletion of AA may have been the cause.

[0031] The use of the formulations of the present invention could be very wide-ranging.

Claims

1. Use of a composition consisting essentially wholly of

a) biologically assimilable eicosapentaenoic acid (EPA), or any appropriate derivative, having a purity of at least

90%, and

b) biologically assimilable arachidonic acid (AA), a precursor of AA, or any appropriate derivative, having a purity of at least 90%,

wherein the ratio of EPA to AA, or precursor of AA, is between 1:1 and 20:1, respectively, with the proviso that if a derivative is used, this is not a phospholipid containing both fatty acids EPA and AA or precursor in the manufacture of a medicament for the treatment of a neurological degenerative disorder.

2. Use according to claim 1, wherein the disease is selected from a degenerative disorder of the brain, Alzheimer's disease and other dementias and Parkinson's disease.

3. Use according to claim 1 or 2 in which the ratio of EPA to AA, or precursor of AA, is between 5:1 and 20:1, respectively.

4. Use according to claim 1, 2 or 3 in which the EPA is provided in a dose of between 100 mg and 10,000mg/day.

5. Use according to any preceding claim in which the composition contains 1 - 4 g EPA and 0.1 - 2.0 g AA or precursor of AA.

6. Use according to any preceding claim in which the composition contains 1.5 - 3 g eicosapentaenoic acid (EPA) or any appropriate derivative, and 0.1 - 2.0 g arachidonic acid (AA), precursor of AA or any appropriate derivative, in any biologically assimilable form.

7. Use according to any preceding claim in which the AA precursor is DGLA.

8. Use according to any preceding claim in which the AA precursor is GLA.

9. Use according to any preceding claim in which the EPA is composed of a triglyceride or ethyl ester which is more than 90% pure.

Patentansprüche

1. Verwendung einer Zusammensetzung, die im Wesentlichen ganz aus Folgendem besteht:

a) einer biologisch assimilierbaren Eicosapentaensäure (EPA) oder einem beliebigen geeigneten Derivat, mit einer Reinheit von wenigstens 90 %, und

b) einer biologisch assimilierbaren Arachidonsäure (AA), einem Vorläufer von AA oder einem beliebigen geeigneten Derivat, mit einer Reinheit von wenigstens 90 %,

wobei das Verhältnis zwischen EPA und AA, oder einem Vorläufer von AA, zwischen 1:1 und 20:1 liegt, unter der Voraussetzung, dass, wenn ein Derivat verwendet wird, dieses kein Phospholipid ist, das die beiden Fettsäuren EPA und AA oder einen Vorläufer enthält, zur Herstellung eines Medikamentes zur Behandlung einer neurologischen Degenerationsstörung.

2. Verwendung nach Anspruch 1, wobei die Krankheit ausgewählt ist aus einer degenerativen Störung des Gehirns, der Alzheimerschen Krankheit und anderen Demenzen und der Parkinsonschen Krankheit.

3. Verwendung nach Anspruch 1 oder 2, wobei das Verhältnis zwischen EPA und AA, oder einem Vorläufer von AA, jeweils zwischen 5:1 und 20:1 liegt.

4. Verwendung nach Anspruch 1, 2 oder 3, wobei die EPA in einer Dosis zwischen 100 mg und 10.000 mg/Tag bereitgestellt wird.

5. Verwendung nach einem der vorherigen Ansprüche, wobei die Zusammensetzung 1 bis 4 g EPA und 0,1 bis 2,0 g AA, oder eines Vorläufers von AA, beinhaltet.

6. Verwendung nach einem der vorherigen Ansprüche, wobei die Zusammensetzung 1,5 bis 3 g Eicosapentaensäure

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(EPA), oder eines beliebigen geeigneten Derivats, und 0,1 bis 2,0 g Arachidonsäure (AA), eines Vorläufers von AA oder eines beliebigen geeigneten Derivats, in einer beliebigen biologisch assimilierbaren Form enthält.

7. Verwendung nach einem der vorherigen Ansprüche, wobei der AA-Vorläufer DGLA ist.
8. Verwendung nach einem der vorherigen Ansprüche, wobei der AA-Vorläufer GLA ist.
9. Verwendung nach einem der vorherigen Ansprüche, wobei die EPA aus einem Triglycerid oder Ethylester besteht, das/der zu mehr als 90 % rein ist.

Revendications

1. Utilisation d'une composition consistant essentiellement entièrement en

- a) acide éicosapentaénoïque (EPA) biologiquement assimilable, ou en un dérivé approprié quelconque, ayant une pureté de 90% au moins, et
- b) en acide arachidonique (AA) biologiquement assimilable, en un précurseur de AA, ou en un dérivé approprié quelconque, ayant une pureté de 90% au moins,

où le rapport d'EPA à AA, ou précurseur de AA, est d'entre 1 : 1 et 20:1, respectivement, à condition que si un dérivé est utilisé ce ne soit pas un phospholipide contenant les deux acides gras, EPA et AA ou le précurseur dans la fabrication d'un médicament pour le traitement d'un trouble neurologique dégénératif.

2. Utilisation selon la revendication 1, dans laquelle la maladie est sélectionnée parmi un trouble dégénératif du cerveau, la maladie d'Alzheimer et autres démences et la maladie de Parkinson.
3. Utilisation selon la revendication 1 ou 2, dans laquelle le rapport d'EPA à AA, ou précurseur de AA, est d'entre 5:1 et 20: 1, respectivement.
4. Utilisation selon la revendication 1,2 ou 3, dans laquelle l'EPA est fourni en une dose d'entre 100 mg et 10.000 mg/jour.
5. Utilisation selon l'une quelconque des revendications précédentes, dans laquelle la composition contient 1 - 4 g d'EPA et 0,1 - 2,0 g de AA ou précurseur de AA.
6. Utilisation selon l'une quelconque des revendications précédentes, dans laquelle la composition contient 1,5 - 3 g d'acide éicosapentaénoïque (EPA) ou d'un dérivé approprié quelconque, et 0,1 g - 2,0 g d'acide arachidonique (AA), de précurseur de AA ou d'un dérivé approprié quelconque, sous une forme biologiquement assimilable.
7. Utilisation selon l'une quelconque des revendications précédentes, dans laquelle le précurseur de AA est du DGLA.
8. Utilisation selon l'une quelconque des revendications précédentes, dans laquelle le précurseur de AA est du GLA.
9. Utilisation selon l'une quelconque des revendications précédentes, dans laquelle l'EPA se compose d'un triglycéride ou d'un ester d'éthyle qui est pur à plus de 90%.

Fig. 1

ESSENTIAL FATTY ACID (EFA) METABOLISM

n-6 series			n-3 series	
18:2n-6	LINOLEIC		ALPHA LINOLENIC	18:3n-3
	↓	Delta-6-desaturation	↓	
18:3n-6	GAMMA-LINOLENIC		STEARIDONIC	18:4n-3
	↓	Elongation	↓	
20:3n-6	DIHOMOGAMMALINOLENIC		EICOSA TETRAENOIC (n-3)	20:4n-3
	↓	Delta-5-desaturation	↓	
20:4n-6	ARACHIDONIC		EICOSAPENTAENOIC	20:5n-3
	↓	Elongation	↓	
22:4n-6	ADRENIC		DOCOSAPENT AENOIC (n-3)	22:5n-3
	↓	Delta-4-desaturation	↓	
22:5n-6	DOCOSAPENTAENOIC (n-6)		DOCOSAHEXAENOIC	22:6n-3